Remarks

Claims 24 to 101 are pending in this application.

I. Rejections under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 24-101 under U.S.C. § 112, first paragraph, allegedly for lack of enablement.

More particularly, the Examiner contends that, "[t]he enablement rejection is not based on the making of the CRCGCL protein or variants of the protein, but on the disclosure enabling the **use** of the protein(s)." (*See,* Paper No. 15, Page 4, Paragraph 3 (emphasis in original).)

Applicants respectfully disagree and traverse.

The Examiner uses a preponderance of "utility rejection" language throughout her response (*see, e.g.,* the Examiner's reference to "specific and substantial utilities" and to the Utility Examination Guidelines at Paper No. 15, Page 5, Paragraph 3); however no formal rejection under 35 U.S.C. § 101 has been made. In response, Applicants submit that since no rejection under 35 U.S.C. § 101 was made, Applicants can either, 1) assume that the Examiner acknowledges that the CRCGCL protein of the invention has a substantial, specific, credible and well-established utility in which case, Applicants respectfully submit that one of ordinary skill in the art would clearly know how to use the invention; or 2) assume that the Examiner was really giving a "lack of utility" rejection in which case, Applicants will show that CRCGCL has a specific, substantial, credible utility. In order to be fully responsive, Applicants address both alternatives herein.

The Examiner asserts to be making a rejection under the how to use requirement of 35 U.S.C. § 112, first paragraph. However, according to M.P.E.P. 2164,07 (I)(A), a 35 U.S.C. § 112, first paragraph utility rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under 35 U.S.C. § 101. In other words, Office personnel should not impose a 35 U.S.C. § 112, first paragraph rejection grounded on a "lack of utility" basis unless a 35 U.S.C. § 101 is proper. In particular, the factual showing needed to impose a rejection under 35 U.S.C. § 101 must be provided if a 35 U.S.C. § 112, first paragraph, rejection is to be imposed on "lack of utility" grounds. *See,* M.P.E.P. §§ 2164.07(I)(A) at 2100-[138-139] (Rev. 1, Feb. 2000). "The how to use prong of section 112 incorporates as a matter of law the requirements of 35 U.S.C. § 101 that the specification

disclose as a matter of fact a practical utility for the invention." (*See, Cross v. Iizuka,* 753 F.2d 1040, 1042-44, 224 USPQ 739, 741-42 (Fed. Cir. 1985) as cited in *In re Karl Ziegler and Heinz Martin* 992 F.2d 1197, 1200; 26 U.S.P.Q.2D (BNA) 1600 (1993)).

A rejection under 35 U.S.C. § 101 is improper when a person of ordinary skill in the art would find credible disclosed features or characteristics of the invention, or statements made by the Applicant in the written description of the invention. *See* M.P.E.P. §§ 2107.01(II), (III) at 2100-[29-31] (Rev. 1, Feb. 2000). In addition, an Applicant need only make *one* credible assertion of utility for the claimed invention to satisfy 35 U.S.C. § 101. *See, e.g., Raytheon v. Roper,* 724 F.2d 951, 958, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown."). *See*, M.P.E.P. at 2100-29. Finding a lack of utility is also improper if a person of ordinary skill in the art would know of a use for the claimed invention at the time the application was filed. M.P.E.P. § 2107.01(II)(B) at 2100-[29-30].

As discussed below, Applicants respectfully submit that the specification satisfies the requirements imposed by 35 U.S.C. § 101 because it teaches specific, substantial, credible and well-established utilities of the claimed invention. Indeed, the Examiner has implied as much since no rejection under 35 U.S.C. § 101 has been imposed. Therefore, pursuant to M.P.E.P. § 2164.07(I)(A), as 35 U.S.C. § 112, first paragraph rejection for "lack of utility" should not be imposed. Moreover, Applicants submit that the full scope of the claims is enabled, and the Examiner's rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement is improper.

In arguing that Applicants' asserted utility is not credible under either 35 U.S.C. § 101 or § 112, first paragraph (*see, In re Brana,* 51 F.3d 1560, 34 U.S.P.Q.2D (BNA) 1436 (1995)), the Examiner must provide a cogent explanation attacking (a) the logic underlying the assertion as seriously flawed or (b) the facts upon which the assertion is based as inconsistent with the logic underlying the assertion. *See, e.g.*, Revised Interim Utility Guidelines Training Materials, p. 5.

In addition, the PTO's own guidelines provide:

> Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the *prima facie* showing of no specific

> and substantial credible utility. If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.

Revised Utility Guidelines, 64 FR at 71442, Part II.B(2)(d)3.

In the instant rejection, the Examiner merely argues that "[t]he enablement rejection is based on assertions of using the protein as a "cytokine receptor", which is not a specific use, or in the general use of regulating the differentiation and/or proliferation of cells" (*see,* Paper No. 15, Page 5, Paragraph 3) , and that "there is not a single working example of any kind of activity, it is not predictable from sequence homology what the activity of the protein would be, and there is limited guidance on how to use the protein" (*see,* Paper No. 15, Page 9, Paragraph 3). The Examiner has failed to provide any countervailing facts or reasoning as to why the disclosed utilities are not specific, substantial and credible, other than by alleging that "[c]ytokine receptors are a large family of proteins that have diverse tissue expression, ligand specificity, and biological activities, and each receptor responds to different cell types." (*See,* Paper No. 15, Page 5, Paragraph 3.) Thus, Applicants assert that the Examiner has not satisfied the burden to make a *prima facie* showing that Applicants' asserted utility is not specific, substantial and credible.

Contrary to the Examiner's contention, Applicants have set forth in the specification statements that clearly and fully describe the function of CRCGCL and explain why Applicants believe the invention is useful. For example, the specification explicitly teaches that CRCGCL has use, for example, as a cytokine receptor (*see, e.g.,* the instant specification at page 1, line 11; page 9, line 19 to 23; and page 10, lines 23-25) which activates the Jak-STAT signal transduction pathway (*see, e.g.,* the specification at page 1, line 24 through page 2, line 5; page 9, line 16, and Example 13 at pages 146-150, particularly page 147, lines 6-8 and line 12), thereby regulating the differentiation and/or proliferation of immune cells (*see, e.g.,* page 96, lines 19 to 24 and page 97, lines 3-5). The specification clearly shows the immune specific expression pattern of CRCGCL (*see, e.g.,* page 8, line 29 through page 9, line 2) and teaches:

> The tissue distribution in only activated T-cells and homology to the cytokine receptors IL2 and IL13 suggests that this protein is a novel member of the cytokine receptor family expressed specifically on T-cells. The tissue distribution of this gene in cells of the immune system suggests that the protein product of this clone would be useful for treatment, prophylaxis and diagnosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, AIDS.

(*See, e.g.*, page 19, lines 23-29.)

Thus, the specification clearly teaches a specific and substantial utility of the disclosed polypeptides as involved in immune cell regulation. The biological role and significance of CRCGCL polypeptides, as well as its specific and substantial utility, are clearly taught by the specification as originally filed. Applicants assert that such characterization is sufficient on its own to constitute a showing of utility.

The Examiner further states that:

> Given the level of skill in the art, if the specific biological activity of the protein were known, it would not require undue experimentation to determine how to use it, however there is no specific biological activity known for this protein.

(*See,* Paper No. 15, Page 4, Paragraph 3 (emphasis in original).)

Applicants provide herewith the executed Declaration of Paul Moore Under 37 C.F.R. § 1.132 which describes data from experiments performed at HGS which affirms the predicted use of CRCGCL in immune cell regulation by binding a cytokine and activating the Jak-STAT signal transduction pathway. As described on page 2, paragraph 4 of the Declaration, a 293T reconstitution cell assay was used to assess whether CRCGCL polypeptides activate the Jak-STAT pathway (as measured by tyrosine phosphorylation), as has been shown for the IL-2R common gamma chain. Increased phosphorylation of STAT5 and Tyk2 was detected using this assay when CRCGCL was cotransfected with IL-7R alpha chain, Jak2, and STAT5 and stimulated with a cytokine, TSLP. The increased phosphorylation of STAT5 and Tyk2 could be inhibited by the addition of a CRCGCL fragment such as the soluble extracellular domain of CRCGCL. The results of these experiments, shown in the Figure provided as Exhibit C, indicate that (1) CRCGCL binds a cytokine and activates the Jak-STAT signal transduction pathway, and (2) the soluble extracellular domain of CRCGCL binds a cytokine and inhibits the Jak-STAT signal transduction pathway.

In addition, as described on page 3, paragraph 5 of the Declaration, flow cytometry was used to measure whether CRCGCL polypeptides bind a cytokine. FACScan analyses were performed on 293T cells which had been transfected with either CRCGCL, IL-7R alpha chain, or IL-2R common gamma chain alone, or in combination with one another, and treated with a FLAG-tagged TSLP molecule bound to an anti-FLAG biotin conjugate and fluorescein isothiocyanate labeled streptavadin. A shift in the mean fluorescent intensity as

measured by FACScan was detected when comparing 293T cells transfected with CRCGCL alone and in combination with IL-7R alpha chain treated with the FLAG-tagged TSLP to the same cells untreated. The results of these experiments, shown in Exhibit D, indicate that CRCGCL binds a cytokine.

In toto, these results demonstrate that, as asserted in the specification as originally filed, that the biological activity of CRCGCL is binding cytokine and activating the Jak-STAT signal transduction pathway. Furthermore, the specification teaches that activation of the Jak-STAT pathway is indicative of proteins involved in cell proliferation, and in this case, immune cells, specifically activated T cells (*see, e.g.,* the specification at page 10, lines 23-25; and page 147, lines 6-8).

Moreover, with regard to the Examiner's assertion that "[t]hese disclosures would be enabling if one of skill in the art knew how to use the protein and assay for activity, but until the protein can be assayed for function, the effect of any amino acid changes cannot be determined" (*see,* Paper No. 15, Page 8, Paragraph 3), Applicants submit that since the CRCGCL polypeptides have a biological activity, for example, binding cytokine and activating the Jak-STAT signal transduction pathway, it would be routine to one of ordinary skill in the art to assay variants of CRCGCL which share 90-95% identity with SEQ ID NO:2.

Applicants submit that it was well-known in the art at the time the present application was filed, and the specification further teaches explicitly that "CRCGCL polynucleotides or polypeptides, or agonists or antagonists of CRCGCL, may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells." *See*, specification, at page 96, lines 19-22. Accordingly, Applicants have contemplated and disclosed therapeutic applications of CRCGCL, for example, treatment of immune system-related disorders, including, but not limited to, immunologic deficiency syndromes, autoimmune disorders, allergic reactions and conditions, graft-versus-host disease, and/or inflammation, consistent with the biological activity of CRCGCL. *See*, *e.g.*, specification, at page 97, line 3 through page 99, line 3.

In addition, Applicants have contemplated and disclosed the therapeutic use of fragments of CRCGCL to treat disease by inhibiting the action of CRCGCL (*see, e.g.,* specification at page 84, lines 29-30; page 113, lines 22-23 and page 117, lines 2-4). The experimental results described above which illustrate the ability of fragments of CRCGCL to

bind a cytokine and inhibit the Jak-STAT signal transduction pathway confirm this asserted use.

Applicants submit that the above asserted utilities for CRCGCL are specific (the vast majority of proteins do not bind cytokine, activate a Jak-STAT signal transduction pathway or modulate immune cell proliferation) and substantial ("the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." (Revised Interim Utility Guidelines Training Materials, p. 6)). In addition, Applicants submit that these utilities are credible.

With regard to these asserted therapeutic activities, Applicants note that there is no need to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. M.P.E.P. § 2107.02 (I) at 2100-[33-34]. All that is required of Applicants is that there be a reasonable correlation between the biological activity and the asserted utility. *See, Nelson v. Bowler*, 626 F.2d 853, 857 (C.C.P.A. 1980). Moreover, "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, *51* F.3d *1560*, *1568* (Fed. Cir. 1995) (emphasis added).

Even assuming, *arguendo*, the Examiner has established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that they have rebutted the Examiner's showing by proffering sufficient evidence to lead one of ordinary skill in the art to conclude that the asserted utilities are more likely than not true. Applicants have directed the Examiner to the specification where clear and specific assertions are made of CRCGCL biological and therapeutic activity and provided experimental evidence confirming the asserted utilities. Thus, as demonstrated above, the specification asserts a specific and substantial utility for the claimed invention. Moreover, as detailed in Applicants' response of January 5, 2001, in light of the detailed teachings in the specification and what was known in the art at the time of invention, this use is enabled; i.e., one of ordinary skill in the art would be readily able to make and would clearly know how to use the claimed invention without undue experimentation using the application as a guide.

For example, since the disclosed or otherwise known methods of making and screening the claimed polypeptides may be used to determine, without undue

experimentation, whether a given polypeptide encompassed by the claims functions, for example, as a cytokine receptor (see, *e.g.,* page 10, lines 23-25), or in activating the Jaks-STAT signal transduction pathway (see, *e.g.,* page 9, line 16, and Example 13, particularly, page 147, line 12), or in regulating the differentiation and/or proliferation of cells (see, *e.g.,* page 9, lines 19-23), or to routinely generate CRCGCL specific antibodies which could be used as immunological probes for differential identification of tissue(s) or cell type(s) (see, *e.g.,* page 10, lines 15-17), or to routinely generate CRCGCL antagonists which would be useful for inhibiting the differentiation and/or proliferation of immune cells (see, *e.g.,* page 84, lines 29-30; page 113, lines 22-23 and page 117, lines 2-4), the enablement requirement is fully satisfied. *In re Wands*, 858 F.2d at 738, 8 U.S.P.Q.2d at 1404; *Ex parte Mark*, 12 U.S.P.Q.2d 1904, 1906-1907 (B.P.A.I. 1989).

In view of the above, Applicants respectfully submit that the presently claimed invention possesses credible, specific and substantial, well-established utilities which constitute patentable utilities under 35 U.S.C. § 101, and therefore also satisfy the 'how to use' requirement of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that the rejection of claims 24-101 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

II. Conclusion

In view of the foregoing amendments and remarks, Applicants believe that this application is now in condition for allowance.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under

37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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